Amendments to the Specification:

Please replace the paragraph beginning at page 3, line 3 with the following amended paragraph:

A wide variety of compounds may be utilized within this regard, including for example (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds hyaluronic acid (HA) ~~HA~~; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID No. 70), P-16 (Sequence ID No. 26); P-32 (Sequence ID no. 71); and GAHWQFNALTVR (Sequence ID No. 72); (b) an antibody which binds any one of domains D1, D2, D3, D4, or, D5 of Receptor Hyaluronic Acid Mediated Motility (RHAMM) ~~RHAMM~~ (e.g., an anti-TAM antibody); (c) a polypeptide fragment which encodes a D1, D2, D3, D4, or, D5 domain of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or delivers and expresses any one of (a), (b), or (c). In one embodiment, the polypeptide can be (a) a first peptide comprised of a hyaluronic acid-binding domain; (b) a hyaladherin polypeptide; (c) a second peptide comprised of a domain from a hyaladherin polypeptide; (d) a hyaladherin-binding polypeptide; (e) a third peptide comprised of a hyaladherin binding domain. Also provided are antibodies which binds to a peptide or polypeptide of (a)-(d); and/or vectors (e.g., gene delivery vectors described below) that expresses a gene encoding a polypeptide as described above or herein. More particular embodiments include methods where a hyaladherin is administered comprised of a RHAMM polypeptide. In a particular embodiment, a first peptide is administered comprised of a sequence selected from the group consisting of SEQ., ID NO: 1-10. In another embodiment, a second peptide is administered comprised of a sequence selected from the group consisting of SEQ. ID NO: 11-20. In another embodiment, a hyaladherin-binding polypeptide comprised of SEQ. ID NO: 21. In still other embodiments, an antibody is administered that binds to a peptide comprised of SEQ. ID NO: 11-20 or an antibody is administered that binds to a RHAMM polypeptide. In a more general embodiment, at least one hyaladherin is administered that is a RHAMM polypeptide.

Please replace the paragraph beginning at page 3, line 27 with the following amended paragraph:

Within other embodiments, the compound to be delivered is a polypeptide comprising less than an entire RHAMM polypeptide (i.e., less than 95kDa or 73kDa~~95 kD or 73 kD~~ molecular weight), and containing at least a portion of RHAMM domains D1 (e.g., aa1-164~~aa1-164~~ of human RHAMM), D2 (the "leucine zipper" domain, e.g., aa 195-122 of human RHAMM), D3 (the "TAM domain", e.g., aa 219-240 of human RHAMM), D4 (the repeat or "R" domain – e.g., aa. 442-546 of mouse and aa. 442-463 of human RHAMM, and amino acid residues 635-645 and amino acid residues 657-666 of human RHAMM~~aa.635-645 and aa. 657-666 RHAMM~~). Equivalent domains in other species may e determined by comparison with the human sequence (see, e.g., Figure 50; SEQ ID NOs:~~SEQ ID Nos.~~ 47 and 48). Within further embodiments, antibodies are provided which bind to any one of the above RHAMM domains (i.e., domains D1, D2, D3, D4, or, D5~~domains D1, D2, D2, D4, or, D5~~). Examples include antibodies to SEQ ID NOs:~~SEQ ID Nos.~~ 14, 17, 23, 24, 26 and 27.

Please replace the paragraph beginning at page 5, line 1 with the following amended paragraph:

In a different aspect, the invention provides cell cultures which are comprised of a transition cells, wherein the transition cells include an activated *erk* kinase signaling activity, a stimulated activating protein-1 (AP-1)~~AP-1~~ binding activity and at least one characteristic selected from the group consisting of: (a) increased podosome formation, (b) increased flux of intracellular or extracellular hyalauronans or hyaladherins, (c) increased expression of a hyaladherin, (d) an inability to form focal adhesions, (e) increased metalloproteinase activity, and (f) increased expression of hyaladherin; wherein measurements of activity or amounts are relative to a normal quiescent cell. In more specific embodiments, the cell culture is comprised of cells transfected with a nucleic acid that overexpresses a hyaladherin. In a still more specific embodiment, the cell culture overexpresses a RHAMM polypeptide. In a related aspect, the invention provides embodiments of an animal cell culture wherein the activated *erk* signaling

activity is less than the activated *erk* signaling activity displayed by normal quiescent cells in response to a growth factor stimulation, wherein the growth factor stimulation is selected from the group consisting of: IL-1 stimulation, PDGF stimulation, and NTF α stimulation.

Please replace the paragraph beginning at page 5, line 28 with the following amended paragraph:

In a different aspect, the invention provides peptide compositions that bind a hyalauronan comprising a peptide of the sequence BX7B (SEQ ID NO:28) wherein B is a basic amino acid and X7 is a sequence of about seven residues selected from any amino acid other than an acidic amino aid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, and with the proviso that the peptide does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK ~~(SEQ ID Nos. 29-44 respectively)~~(SEQ ID NOs: 29-44 respectively).

Please replace the paragraph beginning at page 7, line 17 with the following amended paragraph:

In yet a different aspect, the invention provides methods of identifying a peptide or polypeptide composition for treating a tissue disorder associated with a response-to-injury process or proliferating cells in a mammal comprising the steps of: (a) selecting a sequence from a database screened for sequences comprising a peptide of the sequences BX7B (SEQ ID NO:28) wherein B is a basic amino acid and X7 is a sequence of about seven residues selected from any amino acid other than an acidic amino aid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, (b) preparing a composition comprised of the selected sequence; and (c) testing the prepared composition for the ability to inhibit podosome formation according to other methods taught by this invention, and with the

proviso that the peptide in (a) does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK ~~(SEQ ID Nos. 29-44 respectively)~~(SEQ ID NOs: 29-44 respectively). Within certain embodiments the peptides provided herein can be less than 250, 200, 150, 100, 75, 50, or, 25 amino acids in length.

Please replace the paragraph beginning at page 8, line 19 with the following amended paragraph:

In a further aspect of the present invention polypeptides are provided which comprises or consist only of any one of ~~SEQ ID Nos,~~SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, ~~71, or, 72~~71, or 72. When the polypeptide comprises additional sequences, the polypeptide may, in certain embodiments, be ~~less than 50kd~~less than 50 kDa or ~~20kd of~~20 kDa of molecular weight. In other embodiments, the polypeptide may be less than 60, 50, 40, 30, or 20 amino acids in length. Also provided are such polypeptides that are purified (e.g., free of cells), sterilized, and/or suitable for pharmaceutical use.

Please replace the paragraph beginning at page 8, line 28 with the following amended paragraph:

In yet other aspects of the present invention antibodies are provided which bind to any one of the peptides provided herein, including for example a polypeptide comprising or consisting only of any one of ~~SEQ ID Nos,~~SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, ~~71, or, 72~~71, or 72. Also provided are antibodies such as noted above, which

are purified (e.g., free of cells), sterilized, and/or suitable for pharmaceutical use (e.g., for use in one of the methods described herein).

Please replace the paragraph beginning at page 9, line 7 with the following amended paragraph:

In still another aspect, the invention provides methods for detecting hyalauronic acid in a sample comprising the steps of: (a) incubating the sample with a hyalauronic acid binding peptide comprising a sequence selected from the group consisting of ~~SEQ. ID NO: 1-10~~SEQ ID NOs: 1-10; and (b) detecting an amount of a complex formed between hyalauronic acid and the hyalauronic acid binding peptide. In one embodiment, the detecting employs an antibody that specifically binds to the hyalauronic acid binding peptide.

Please replace the paragraph beginning at page 10, line 25 with the following amended paragraph:

Figure 8 shows the increased expression levels of c-fos and c-jun gene in cells overexpressing RHAMM regardless whether grown on poly L-lysine (PL) ~~PL~~ or fibronectin (FN) ~~FN~~.

Please replace the paragraph beginning at page 10, line 27 with the following amended paragraph:

Figure 9A and 9B are northern blots probed with gelatinase B, stromelysin, timp-1, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) complementary DNA (cDNA) ~~GAPDH CDNAS~~.

Please replace the paragraph beginning at page 11, line 3 with the following amended paragraph:

Figures 11A and 11B are northern analysis of interleukin-1 (IL-1) ~~IL-1~~ and tumor necrosis factor (TNF) ~~TNF~~-alpha induction of *c-fos*.

Please replace the paragraph beginning at page 11, line 9 with the following amended paragraph:

Figure 14A, 14B, and 14C are graphs which illustrate the ~~relationship of RHAM~~relationship of RHAMM, *erk* activity and podosome formation. Figures 14D, 14E, and 14F are photos which supplement this data.

Please replace the paragraph beginning at page 11, line12 with the following amended paragraph:

Figure 15 A is a bar graph which shows a comparison of RHAMM expression at a cell surface. Figure 15B provides the sequence of various RHAMM peptides ~~(SEQ ID Nos. 14-20)~~ (SEQ ID NOs: 14-20).

Please replace the paragraph beginning at page 12, line 3 with the following amended paragraph:

Figure 24A and 24B are a graph, and a blot, respectively, which show the effects of exon 4 antibody and leucine zipper peptide (LZP) ~~LZP~~ on the formation of podosomes.

Please replace the paragraph beginning at page 12, line 10 with the following amended paragraph:

Figure 27 is a bar graph which shows that treatment of injured cells with P-peptide (CSTMMSRSHKTRSHHV – SEQ ID NO:26~~Seq. ID. No. 26~~) inhibits migration of human foreskin fibroblast (HFF) ~~HFF~~ cells.

Please replace the paragraph beginning at page 12, line 12 with the following amended paragraph:

Figure 28 is a bar graph which shows velocity of cells after addition of peptide ~~aa423-432 (Sequence ID No. 24)~~amino acid residues 423-432 (SEQ ID NO: 24).

Please replace the paragraph beginning at page 12, line 24 with the following amended paragraph:

Figure 34 is a bar graph which illustrates the motility of bronchoalveolar lavage (BAL) ~~BAL~~ cells four days after injury in response to administration of RHAMM peptides.

Please replace the paragraph beginning at page 13, line 21 with the following amended paragraph:

Figure 48A is a schemata showing domains of various RHAMM polypeptides required for podosome formation and activation of *erk* kinase signaling and Figure 48B is a protein gel showing that intracellular RHAMMv4 binds to extracellular signal-regulated kinase (ERK). ~~ERK kinase.~~

Please replace the paragraph beginning at page 13, line 24 with the following amended paragraph:

Figure 49 shows (A) a partial amino acid (SEQ ID NO:46) and nucleotide sequence (SEQ ID NO:45) of a RHAMM binding protein (RABP) isolated using a phage two hybrid system; (B) a Northern blot of RABP expression in transition cells; (C) a Western blot of transitional cell lysate indicating that RABP is a 60 kDa protein; and (D) a fluorescence-activated cell sorting (FACS) ~~FACS~~ analysis illustrating that RABP is present on the cell surface.

Please replace the paragraph beginning at page 20, line 26, with the following amended paragraph:

For example, within one aspect of the invention methods of identifying a peptide or polypeptide composition for treating a tissue disorder associated with a response-to-injury process, or, the proliferation of cells in a mammal is provided, comprising the general steps of: (a) selecting a sequence from a database screened for sequences comprising a peptide of the sequence BX7B (SEQ ID NO:28) wherein B is a basic amino acid, and X7 is a sequence of

about seven residues is selected from any amino acid other than an acidic amino acid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, (b) preparing a composition comprised of the selected sequence; and (c) testing the prepared composition for the ability to inhibit podosome formation. Within certain embodiments, the peptide in (a) does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK ~~(SEQ ID Nos. 29-44 respectively)~~(SEQ ID NOs: 29-44 respectively).

Please replace the paragraph beginning at page 22, line 1, with the following amended paragraph:

In still another aspect, the invention provides methods for detecting hyalauronic acid in a sample comprising the steps of: (a) incubating the sample with a hyalauronic acid binding peptide comprising a sequence selected from the group consisting of ~~SEQ. ID NO: 1-10~~SEQ ID NOs: 1-10; and (b) detecting an amount of a complex formed between hyalauronic acid and the hyalauronic acid binding peptide. In one embodiment, the detecting employs an antibody that specifically binds to the hyalauronic acid binding peptide.

Please replace the paragraph beginning at page 24, line 12, with the following amended paragraph:

b. Peptide mimetics

Numerous peptide mimetics may also be utilized within the present invention, including for example peptides such as:

SEQ. ID. NO: 1 (H4-5)B3;

SEQ. ID. NO: 2 (H4-5)BXBBXB;

SEQ. ID. NO: 3 (H4-5)BXBXBBB;

SEQ. ID. NO: 4 (H4-S)BXBBB; and

SEQ. ID. NO: 5 (H4-5)BXBB

where B is either lysine (K)or ~~arginine (R~~arginine (R) and X is a hydrophobic or neutral amino acid (i.e., L, V, Q, S) and H represents a series of amino acids such that an alpha helix is formed, as determined by NN-predict EMBL protein analysis. This need not be an amphipathic or coiled coil helix but such would also be suitable. Specific examples of sequences fitting these motifs that have been analyzed for effectiveness on podosome include the following:

SEQ. ID. NO: 6 MMTVLKR;

SEQ. ID. NO: 7 MMTVLKVKRLR;

SEQ. ID. NO: 8 MMTVLKVKVKRK;

SEQ. ID. NO: 9 MMTVLKVRKR; and

SEQ. ID. NO: 10 MMTVLKVRK.

Please replace the paragraph beginning at page 26, line 2, with the following amended paragraph:

Although various genes (or portions thereof) have been provided herein, it should be understood that within the context of the present invention, reference to one or more of these genes includes derivatives of the genes that are substantially similar to the genes (and, where appropriate, the proteins (including peptides and polypeptides) that are encoded by the genes and their derivatives). As used herein, a nucleotide sequence is deemed to be "substantially similar" if: (a) the nucleotide sequence is derived from the coding region of the above-described genes and includes, for example, portions of the sequence or allelic variations of the sequences discussed above, (b) the nucleotide sequence is capable of hybridization to nucleotide sequences of the present invention under moderate, high or very high stringency (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 2nd ed., Cold Spring Harbor Laboratory Press, NY, 1989); or (c) the DNA sequences are degenerate as a result of the genetic code to the DNA sequences defined in (a) or (b). Further, the nucleic acid molecule disclosed herein includes both complementary and non-complementary sequences, provided the sequences otherwise meet the criteria set forth herein. Within the context of the present invention, high stringency means

standard hybridization conditions (*e.g.*, (5X SSPE (SSPE comprises 0.15M NaCl, 10mM $NaHaPo_4$, 1mM EDTA, pH 7.4) ~~5XSSPE~~, 0.5% sodium dodecyl sulfate (SDS) ~~SDS~~ at 65°C, or the equivalent).

Please replace the paragraph beginning at page 28, line 12, with the following amended paragraph:

Nucleic acid molecules which encode proteins of the present invention may also be constructed utilizing techniques of polymerase chain reaction (PCR) ~~PCR~~ mutagenesis, chemical mutagenesis (Drinkwater and Klinedinst, *PNAS 83*:3402-3406, 1986), by forced nucleotide misincorporation (*e.g.,* Liao and Wise *Gene 88*:107-111, 1990), or by use of randomly mutagenized oligonucleotides (Horwitz et al., *Genome 3*:112-117, 1989).

Please replace the paragraph beginning at page 32, line 5, with the following amended paragraph:

Monoclonal antibodies may also be readily generated from hybridoma cell lines using conventional techniques (*see* U.S. ~~Patent Nos.~~Patent NOs: RE 32,011, 4,902,614, 4,543,439, and 4,411,993; *see also Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988). Briefly, within one embodiment, a subject animal such as a rat or mouse is injected with an antigen of interest or a portion thereof. The protein may be administered as an emulsion in an adjuvant such as Freund's complete or incomplete adjuvant in order to increase the immune response. Between one and three weeks after the initial immunization the animal is generally boosted ~~and may tested~~and may be tested for reactivity to the protein utilizing well-known assays. The spleen and/or lymph nodes are harvested and immortalized. Various immortalization techniques, such as mediated by Epstein-Barr virus or fusion to produce a hybridoma, may be used. In a preferred embodiment, immortalization occurs by fusion with a suitable myeloma cell line (*e.g.*, NS-1 (ATCC No. T1B 18), and P3C63 – Ag 8.653 (ATCC No. CRL 1580) to create a hybridoma that secretes monoclonal antibody. The preferred fusion partners do not express endogenous antibody genes. Following fusion, the cells

are cultured in medium containing a reagent that selectively allows for the growth of fused spleen and myeloma cells such as HAT (hypoxanthine, aminopterin, and thymidine) and are subsequently screened for the presence of antibodies that are reactive against the desired antigen of interest. A wide variety of assays may be utilized, including for example countercurrent immuno-electrophoresis, radioimmunoassays, radioimmunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, western blots, immunoprecipitation, inhibition or competition assays, and sandwich assays (*see* U.S. ~~Patent Nos.~~Patent NOs: 4,386,110 and 4,486,530; *see also Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988).

Please replace the paragraph beginning at page 34, line 11, with the following amended paragraph:

Proteins or polypeptides of the present invention may be readily expressed in a variety of host cells or organisms. For protein production and purification, proteins are preferably secreted and produced in bacteria, such as *E. coli*, for which many expression vectors have been developed and are available. Other suitable host organisms include other bacterial species (*e.g.*, *Bacillus,* and eukaryotes, such as yeast (*e.g., Saccharomyces cerevisiae)*, mammalian cells (*e.g.*, Chinese hamster ovary (CHO) ~~CHO~~ and COS-7), plant cells and insect cells (*e.g.*, Sf9). Vectors for these hosts are well known.

Please replace the paragraph beginning at page 35, line 9, with the following amended paragraph:

The plasmids used herein for expression of a desired protein or polypeptide include a promoter designed for expression of the proteins in a bacterial host. Suitable promoters are widely available and are well known in the art. Inducible or constitutive promoters are preferred. Such promoters for expression in bacteria include promoters from the T7 phage and other phages, such as T3, T5, and SP6, and the trp, lpp, and lac operons. Hybrid promoters (*see,* U.S. Patent No. 4,551,433), such as tac and trc, may also be used. Promoters for expression in

eukaryotic cells include the P10 or polyhedron gene promoter of baculovirus/insect cell expression systems (*see e.g.*, U.S. ~~Patent Nos.~~Patent NOs: 5,243,041, 5,242,687, 5,266,317, 4,745,051, and 5,169,784), mouse mammary tumor virus (MMTV), long term repeat (LTR), rous sarcoma virus (RSV) LTR, simian virus 40 (SV40), ~~MMTV LTR, RSV LTR, SV40~~, metallothionein promoter (*see, e.g.,* U.S. Patent No. 4,870,009) and other inducible promoters. For expression of the proteins, a promoter is inserted in operative linkage with the coding region of the desired protein or polypeptide.

Please replace the paragraph beginning at page 35, line 21, with the following amended paragraph:

The promoter controlling transcription of the desired protein may be controlled by a repressor. In some systems, the promoter can be derepressed by altering the physiological conditions of the cell, for example, by the addition of a molecule that competitively binds the repressor, or by altering the temperature of the growth media. Preferred repressor proteins include, but are not limited to the *E. coli* lacI repressor responsive to isoproplß-D-1-thiogalactopyranoside (IPTG) ~~IPTG~~ induction, the temperature sensitive λcI857 repressor, and the like. The *E. coli* lacI repressor is preferred.

Please replace the paragraph beginning at page 37, line 26, with the following amended paragraph:

Within related aspects of the present invention, proteins of the present invention may be expressed in a transgenic animal whose germ cells and somatic cells contain a gene which encodes the desired protein and which is operably linked to a promoter effective for the expression of the gene. Alternatively, in a similar manner transgenic animals may be prepared that lack the desired gene (*e.g.*, "knockout" mice). Such trangenics may be prepared in a ~~variety~~variety of non-human animals, including mice, rats, rabbits, sheep, dogs, goats and pigs (*see* Hammer et al., *Nature 315*:680-683, 1985, Palmiter et al., *Science 222*:809-814, 1983, Brinster et al., *Proc. Natl. Acad. Sci. USA 82*:4438-4442, 1985, Palmiter and Brinster, *Cell*

41:343-345, 1985, PCT Publication No. WO 99/01164, and U.S. ~~Patent Nos.~~Patent NOs: 5,175,383, 5,087,571, 4,736,866, 5,387,742, 5,347,075, 5,221,778, 5,162,215; 5,545,808; 5,741,957; 4,873,191; 5,780,009; 4,736,866; 5,567,607; 5,633,076 and 5,175,384). Briefly, an expression vector, including a nucleic acid molecule to be expressed together with appropriately positioned expression control sequences, is introduced into pronuclei of fertilized eggs, for example, by microinjection. Integration of the injected DNA is detected by blot analysis of DNA from tissue samples. It is preferred that the introduced DNA be incorporated into the germ line of the animal so that it is passed on to the animal's progeny. Tissue-specific expression may be achieved through the use of a tissue-specific promoter, or through the use of an inducible promoter, such as the metallothionein gene promoter (Palmiter et al., 1983, *ibid*), which allows regulated expression of the transgene.

Please replace the paragraph beginning at page 38, line 20, with the following amended paragraph:

A wide variety of gene delivery vectors may be utilized to deliver and/or express a desired gene of interest in host cells. For example, within one aspect of the present invention, retroviral gene delivery vehicles may be utilized. Briefly, retroviral gene delivery vehicles of the present invention may be readily constructed from a wide variety of retroviruses, including for example, B, C, and D type retroviruses as well a spumaviruses and lentiviruses (see RNA tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985). Such retroviruses may be readily obtained from depositories or collections such as the American Type Culture Collection ("ATCC"; Rockville, Maryland), or isolated from known sources using commonly available techniques. Representative examples of retroviral gene delivery vectors are described in more detail in EP 0,415,731; PCT ~~Publication Nos.~~Publication NOs: WO 90/07936; WO 91/0285, WO 9311230; WO 9310218, WO 9403622; WO 9325698; WO 9325234; and U.S. ~~Patent Nos.~~Patent NOs: 5,219,740, 5,716,613, 5,851,529, 5,591,624, 5,716,826, 5,716,832, and 5,817,491.

Please replace the paragraph beginning at page 39, line 5, with the following amended paragraph:

Other suitable gene delivery vectors can be generated from alphaviruses (see *e.g.*, U.S. ~~Patent Nos.~~Patent NOs: 5,091,309 and 5,217,879, 5,843,723, and 5,789,245), recombinant adenoviral vectors (see *e.g.*, U.S. Patent No. 5,872,005), and numerous other viruses such as pox viruses, such as canary pox virus or vaccinia virus (Fisher-Hoch et al., *PNAS 86*: 317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al, *Vaccine 8*:17-21, 1990; U.S. ~~Patent Nos.~~Patent NOs: 4,603,112, 4,769,330 and 5,017,487; WO 89/01973); SV40 (Mulligan et al., *Nature 277*:108-114, 1979); influenza virus (Luytjes et al., *Cell 59*:1107-1113, 1989; McMichael et al., *N. Eng. J. Med. 309*:13-17, 1983; and Yap et al., *Nature 273*:238-239, 1978); herpes (Kit, *Adv. Exp. Med. Biol. 215*:219-236, 1989; U.S. Patent No. 5,288,641); HIV (Poznansky, *J. Virol. 65*:532-536, 1991); measles (EP 0 440,219); Semliki Forest Virus, and coronavirus as well as other viral systems (*e.g.*, EP 0,440,219; WO 92/06693; U.S. Patent No. 5,166,057).

Please replace the paragraph beginning at page 39, line 17, with the following amended paragraph:

In addition to the above viral-based vectors, numerous non-viral gene delivery vehicles may likewise be utilized within the context of the present invention. Representative examples of such gene delivery vehicles include direct delivery of nucleic acid expression vectors or naked DNA alone (see *e.g.*, U.S. ~~Patent Nos.~~Patent NOs: 5,814,482 and 5,580,859), polycation condensed DNA linked or unlinked to killed adenovirus (Curiel et al., *Hum. Gene Ther. 3*:147-154, 1992), DNA ligand linked to a ligand (Wu et al., *J. of Biol. Chem 264*:16985-16987, 1989), and nucleic acid containing liposomes (e.g., WO 95/24929 and WO 95/12387).

Please replace the paragraph beginning at page 40, line 5, with the following amended paragraph:

Within one embodiment, the polypeptide BX7B (SEQ ID NO:28) comprises a polypeptide wherein B is a basic amino acid and X7 is a sequence of about seven residues selected from any amino acid other than an acidic amino acid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, and with the proviso that the peptide does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK ~~(SEQ ID Nos. 29-44 respectively)~~(SEQ ID NOs: 29-44 respectively).

Please replace the paragraph beginning at page 40, line 14, with the following amended paragraph:

In one embodiment, the polypeptide can be (a) a first peptide comprised of a hyalauronic acid-binding domain; (b) a hyaladherin polypeptide; (c) a second peptide comprised of a domain from a hyaladherin polypeptide; (d) a hyaladherin-binding polypeptide; (e) a third peptide comprised of a hyaladherin binding domain. Also provided are antibodies which binds to a peptide or polypeptide of (a)-(d); and/or vectors (e.g., gene delivery vectors described below) that expresses a gene encoding a polypeptide as described above or herein. In a particular embodiment, peptides are provided comprised of a sequence selected from the group consisting of ~~SEQ. ID NO: 1-20~~SEQ ID NOs: 1-20. In another embodiment, a hyaladherin-binding polypeptide comprised of ~~SEQ. ID No: 21~~SEQ ID NO: 21.

Please replace the paragraph beginning at page 40, line 23, with the following amended paragraph:

Within particularly preferred embodiments of the invention, the compound is an antibody. Representative examples of antibodies suitable for use within the present invention include antibodies to domain D1 of RHAMM amino acids 1-164 of human RHAMM (including for example: sequences recognizing the murine D1 sequence, aa. 97-111 – QERGTQKRIQDME

(SEQ ID NO:21); and sequences recognizing human RHAMM, aa 151-164 – LKSKFSENGNQKNL (SEQ ID NO:18)); antibodies to domain D2 of RHAMM – the "leucine zipper" domain of human RHAMM from aa 195-222; antibodies which recognize the domain D3 –the TAM domains of RHAMM (aa 219-240 of the human RHAMM Sequence, including antibodies which recognize the sequence VSIEKEKIDEK (SEQ ID NO:49)); domain D4 (repeat or "R" domain – aa 442-546 for mouse, and aa 442-463 for human) and domain D5 (HA binding domain, including two domains: aa 721-730 and aa 742-752 for mouse; aa 635-645 and aa 657-666 for human). In other embodiments, antibodies are provided which bind to a polypeptide comprised of ~~SEQ. ID NO: 11-20~~SEQ ID NOs: 11-20.

Please replace the paragraph beginning at page 41, line 8, with the following amended paragraph:

As utilized herein, reference may be made to the human sequence of RHAMM for identification of the domains. However, the domains can be identified and specific antibodies generated for other species, such as for example, mouse. Figure 50 (~~SEQ ID Nos.~~SEQ ID NOs: 47 and 48) provides the amino acid sequence of human and mouse RHAMM (see PCT publication No. WO 97/38098 and Genbank ~~Accession Nos.~~Accession NOs: AAC52049 & Q00547). As utilized herein, it should be understood that antibodies "bind" to the above sequence if they do so with a K_d of at least 10^{-7} M (moles /liter) (see "antibodies" above).

Please replace the paragraph beginning at page 55, line 15, with the following amended paragraph:

Inflammatory dermatological diseases, such as psoriasis, are very common, affecting as many as 1 to 2% of the people in the United States. It is often associated with arthritis, myopathy, spondylitic heart disease and acquired immune deficiency syndrome (AIDS) ~~AIDS~~. Psoriasis is a chronic inflammatory disease characterized by keratinocyte hyperproliferation and a distinct inflammatory pattern that is dependent on the type of psoriasis. The underlying

pathogenesis involves three predominant and interdependent biologic processes: inflammation, epidermal hyperproliferation, and altered differentiation with parakeratosis.

Please replace the paragraph beginning at page 55, line 20, with the following amended paragraph:

The homeostasis of the epidermis depends on the balance of growth regulatory signals, which appear to be altered in psoriasis. The epidermis serves a number of important barrier functions against protein and water loss, entry of microorganisms, physiochemical trauma including ultra violet (UV) ~~UV~~. The squamous epithelium undergoes terminal differentiation resulting in an insoluble cornified envelope providing an important barrier. Keratinocyte proliferation takes place in the basal layer and migrate through the epidermis where differentiation specific proteins such as involucrin and keratins are expressed. Normal epidermis represents a normal balance between kaeratinocyte production in the basal layer and corneocyte shedding at the skin surface. Upon wounding or psoriasis, there are rapid increases in the proliferation of keratinocytes.

Please replace the paragraph beginning at page 60, line 18, with the following amended paragraph:

In cases where there are more extensive surface wounds such as burns, abscess formation, inflammatory ulceritis, the reparative process is also more extensive. The larger tissue defects have greater cell loss, more fibrin and more inflammation, increased amounts of granulation tissue and wound contraction involving myofibroblasts. Regardless of the wound, the mechanisms of responsible for the processes of healing described above are similar. Wound healing is ultimately regulated by growth factors and cytokines that balance matrix synthesis and degradation locally. Collagen synthesis is a key component of wound healing and provides the tensile strength required closing of the incision. The type of collagen produced is dependent on the tissue repaired, and changes in the type of collagen may lead to dysfunction tissue. Collagen synthesis is stimulated early in tissue repair by factors such as platelet derived growth factor

(PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF) ~~PDGF, FGF, and TGF~~. On the other hand, degradation of collagen fibrils and other matrix molecules are also important. The degradative enzymes involved during wound healing include matrix metalloproteinases, neutrophil elastase, cathepsin G, kinins, plasmin and other enzymes. Inflammatory and local cells produce these enzymes. Degradation may aid in the remodeling of the connective tissue repair. If the inflammatory destructive processes are suppressed, then it is more likely to achieve a more rapid formation of the connective tissues and decrease the accumulation of scar tissue.

Please replace the paragraph beginning at page 63, line 24, with the following amended paragraph:

Thus, within one embodiment methods are provided for inflammatory / proliferative diseases associated with surgical procedures or intervention (e.g., restonosis, stenosis, medical implants and the like), comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides ~~comprising 15 (Sequence ID No.70)~~comprising P-15 (SEQ ID NO:70), P-16 ~~(Sequence ID No. 26)~~(SEQ ID NO:26); P-32 ~~(Sequence ID no. 71)~~(SEQ ID NO:71); and GAHWQFNALTVR ~~(Sequence ID No. 72)~~(SEQ ID NO:72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than ~~95 kD or 73 kd~~95 kDa or 73 kDa, comprising all or a portion of domains D1, D2, D3, D4, or D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 71, line 20, with the following amended paragraph:

As noted above, the present invention also provides a variety of pharmaceutical compositions, comprising one of the above-described molecules with a pharmaceutically or

physiologically acceptable carrier, excipients or diluents. Generally, such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the therapeutic agent with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as ethylenediamine tetraacetic acid (EDTA) ~~EDTA~~, gluthathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents.

Please replace the paragraph beginning at page 73, line 5, with the following amended paragraph:

In disease or injury, mediators such as cytokines, growth factors and genetic mutations activate a myriad of responses leading in increased expression of AP-1 dependent genes (Figure 1). These genes are required for cell proliferation, migration, inflammation, tissue destruction and abnormal tissue remodeling. The activation of the AP-1 pathway occurs through the activation of the mitogen-activated protein (MAP) ~~MAP~~ kinase. The present invention discloses that in normal cells the activation of the AP-1 pathway by cytokines and other mediators is restricted and thus genes involved in disease cannot be induced significantly. ~~Further~~Further, this restriction is a result of the lack of ERK-1 activation in normal cells (Figure 2). Normal cells must undergo a series of transitional stages to form a diseased state cell containing focal adhesions and is then responsive to inflammatory mediators. Transition stage cells provided by the present invention constitutively form podosomes and are unable to establish focal adhesions. Sustained formation of podosomes leads to the formation of focal adhesions and results in a diseased state (Figure 3). The present invention further discloses a requirement for focal adhesions for maximal activation of *erk* kinase in response to growth factors and cytokines. Cellular response-to-injury processes including growth factor mediated responses which lead to cellular proliferation, migration, production of destructive enzymes and abnormal tissue remodeling are characterized by a maximal activation of the *erk* kinase signaling pathway. To

demonstrate that this response requires the presence of focal adhesions, the response to IL-1 induction of *erk* kinase signaling was measured in cells grown under conditions permitting or preventing the formation of focal adhesions.

Please replace the paragraph beginning at page 73, line 26, with the following amended paragraph:

Cells were either plated without serum on culture dishes precoated at 4°C overnight with 25 μg/ml fibronectin which permits formation of focal adhesions or with 100 μg/ml poly-l-Lysine which prevents formation of focal adhesions. Formation of focal contacts was detected by positive immunofluorescence of the marker protein, vinculin. Activation of *erk* kinase signaling in comparison to other MAP kinase signaling pathways regulated by growth factors was estimated by detection of proteins phsophoryalted by components of the differing signaling cascades. Phosphorylation of myelin basic protein (MBP) is an indicator of *erk* kinase signaling, phsophoryaltion of glutathione-S-transferase (GST)-*c-jun*~~GST-*c-jun*~~ is an indicator of *jnk* signaling, and phsophoryaltion of GST-ATF2 is an indicator of p38 kinase signaling cascade. Results of this analysis is shown in Figure 4.

Please replace the paragraph beginning at page 75, line 19, with the following amended paragraph:

For the preparation of nuclear extracts, cells were washed twice with PBS (phosphate-buffered saline) and lysed with 1 ml buffer (10 mM Tris-Cl, pH 7.5, 10 mM NaCl, 3 mM $MgCl_2$, 0.5% Nonidet P-40, 0.5 mM phenylmethylsulfonyl fluoride (PMSF). Cells were scraped into an eppendorf tube and put on ice for 10 min. The nuclei were collected after centrifugation at 5000 rpm for 10 min. Nuclear proteins were prepared by resuspending the nuclei in buffer 2 (20 mM Hepes, pH7.9, 5 mM $MgCl_2$, 0.2 mM EDTA, 1 mM ~~DTT~~ dithiothreitol (DTT), 300 mM NaCl, 20% glycerol, 0.5 mM PMSF), after centrifugation at 14,000 rpm for 10 min., supernatant was harvested. Double-stranded AP-1 oligonucleotide (Santa Cruz, Biotech, Inc.) was end-labeled with [γ-^{32}P] ATP (DuPont NEN) using T4 polynucleotide kinase (Pharmacia). Labeled probe

was separated from free nucleotide through a Sephadex G-50 mini-spin column (Pharmacia). DNA-protein binding was performed by mixing 10 μg of nuclear extract with ^{32}P-labeled double-stranded AP-1 consensus oligonucleotide in a total volume of 20 μl containing mM Hepes, pH 7.9, 1 mM $MgCl_2$, 4% Ficoll, 0.5 mM DTT, 50 mM KCl, 1 mM EDTA, 2 μg poly(dI·dC) and 1 mg/ml BSA for 45 min on ice. The DNA protein complex was separated on a 4% native polyacrylamide gel using 0.5X tris-borate-EDTA buffer at 150 V. Gels were then dried and autoradiographed.

Please replace the paragraph beginning at page 81, line 27, with the following amended paragraph:

The amount of ERK2 and phosphorylated MAPK were detected from the total extracts by western blot analysis and ECL chemiluminescence system. Lysates of 25 μg total protein were resolved by 10% ~~SDS-PAGE~~ sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS_PAGE) and transferred onto nitrocellulose membrane (BioBlot, Costar) using Trans-Blot® Semi-Dry Electrophoretic Transfer Cell (BioRad) with a transfer-blotting buffer containing 20 mM Tris, 150 mM glycine, 0.01% SDS and 20% methanol. The filters were blocked for non-fat skim milk in TBS-T (20 mM Tris, pH 7.5, 150 mM NaCl and 0.1% Tween 20) at 4°C overnight. The membranes were then probed with phospho-specific anti-p44/p42 MAP kinase antibody (New England BioLabs, Inc) by incubation at room temperature for 1.5 h. After washing three times with TBS-T for 30 min, blots were incubated with horseradish peroxidase conjugated anti-rabbit antibodies (NEB) for 1 h. The filters were washed three times for 30 min and visualized on X-ray film with chemiluminescence detection method (NEB).

Please replace the paragraph beginning at page 88, line 11, with the following amended paragraph:

Briefly, LR21 cells were plated in DMEM with 10% serum at 70-80% density and allow to grow for 8h. Cells were then washed twice with PBS. After being washed cells were incubated in cell dissociation medium to detach from the plates. Cell dissociation medium was

harvested and centrifuged at 1000 rpm's for 3.5 min~~31/2 min~~. Then, cells were plated at fibronectin-coated coverslips at 50% density in DMEM supplemented with 10% FBS. Cells ~~were allow~~were allowed to grow for up to 9h. Plates were then divided into 4 groups and treated in the following manner: control group was treated with 50 μg/ml of BSA in DMEM supplemented with 10% FBS; second group was treated with 50 μg/ml of v4 antibody; third group was treated with 100 mg/ml of LZP and the fourth group was treated with combination of v4 antidoby and LZP at the same concentrations as they were used in separate treatments. Cells were kept with the proteins for 30 min and they were fixed with 3% paraformaldehyde. Cells were stained with cortactin (dil.1:100) for 1h. Subsequently, cells were washed with 1% ~~BSA~~ bovine serum albumin (BSA) in ~~PBS~~ phosphate buffered saline (PBS) and stained with Texas-red mouse IgG (dil. 1:100). Staining of the cells was examined by confocal microscope.

Please replace the paragraph beginning at page 92, line 4, with the following amended paragraph:

Figure 26 illustrates that HA binding peptides including artificial mimics of hyalauronan binding domains of RHAMM are able to block cell motility in podosome forming cells while scrambled peptides do not. Figure 26A provides the sequence of several artificial HA binding peptides of the formula BX7B (SEQ ID NO:28) discussed above. Panel B shows that each of these peptides are able to block cell motility when administered to cells. Panel C shows that an HA binding peptide according to one of the general structures provided in ~~SEQ ID NO: 1-5~~SEQ ID NOs: 1-5, and more particularly having one of the structures provided in ~~SEQ. ID NOS. 6-10~~SEQ ID NOs: 6-10 is even more effective in blocking cell motility and that a scrambled version of this peptide is not.

Please replace the paragraph beginning at page 92, line 29, with the following amended paragraph:

In animal models of skin wounding, expression of an active (73 kDa) RHAMM form is transiently increased early after injury and this elevated expression occurs in most cell types

present in the wound site. A specific domain within RHAMM (D5) that is responsible for interactions of hyalauronan with cell surface RHAMM and erk1 binding to intracellular RHAMM was identified and utilized to develop a peptide mimetic reagent (p-16), which blocks function of cell surface RHAMM. Another RHAMM sequence consisted of 9 amino acid residues~~consisted of 9AA~~ (423-432) which was also tested in the following experiment.

Please replace the paragraph beginning at page 93, line 7, with the following amended paragraph:

The objectives of ~~following~~the following experiment were to test the abilities of two RHAMM synthetic peptides to inhibit migration of human fibroblasts. One experimental model tested a 16 amino acid RHAMM peptide mimetic (P-peptide) to inhibit migration of Human Foreskin Fibroblast (HFF) through the wound gap. Another peptide consisted ~~of 9 AAs~~of 9 amino acids (RHAMM sequence, ~~423-432 AA was~~aa. 423-432 was also tested in regards of cell locomotion of human fibroblasts.

Please replace the paragraph beginning at page 93, line 14, with the following amended paragraph:

Human fibroblasts were seeded at 5 X 10^5 cells/well in 6 well plates using α-MEM supplemented with glucose and 10% ~~FBS~~ fetal bovine serum (FBS). After being 6 hours in the culture (80-90% confluency), cells were injured with the single edge cell scraper (one injury/dish). Cells were washed twice with PBS and treated with two different concentrations of P-peptide (10 μg and 100 μg) for 15 h. Untreated cells served as control. Following 15 hours of incubation, images were taken using a 5X modulation objective (Zeis, Germany) attached to the Zeiss Axiovert 100 inverted microscope equipped with Hoffman Modulation contrast optical filters (Greenvale, NY). The number of migrated cells in each image was counted choosing the ~70% of the middle of each injury. Statistically significant ($P<0.05$) differences between means were assessed by the unpaired Student's t-test method, using Microsoft Excel '97 software.

Please replace the paragraph beginning at page 93, line 26, with the following amended paragraph:

To quantify the effect of RHAMM sequence ~~(423-432-AA)~~(aa. 423-432) to alter velocity of cell locomotion human fibroblasts were seeded on T-12.5 fibronectin coated flasks using α-MEM supplemented with glucose and 10% FBS. 2.5×10^4 cells were seeded and cells incubated for 4 hrs at 37°C. After incubation time cells were treated with increasing concentrations of RHAMM sequence peptide (~~423-432-AA~~aa. 423-432, 0.1, 1.0, 5.0, 10 and 50 ng/ml) and cell locomotion was monitored over the period of 16 hrs on 37°C using 10X modulation objective (Zeiss, Germany) attached to a Zeiss Axiovert 100 inverted microscope equipped with Hoffman Modulation contrast optical filters (Greenvale, NY). Cell images were captured with a ~~CCD~~ charge coupled device (CCD) video camera module attached to a Hamamatsu CCD camera controller. Motility was assessed using Northern Exposure 2.9 image analysis software (Empix Imaging, Mississauga, Ontario). Nuclear displacement of 7 – 10 cells was measured and data were subjected to statistical analysis. Statistically significant ($P<0.05$) differences between means were assessed by the unpaired Student's T-test method, performed using Microsoft Excel "97 software.

Please replace the paragraph beginning at page 94, line13, with the following amended paragraph:

Results are shown in Figures 27 and 28. Briefly, Figure 27 shows that treatment of injured cells with 100 μg/ml of P-peptide inhibited migration of HFF cells approximately 4 fold compared to control cells ($P<0.01$). Lower concentration (10μg/ml) of P-peptide didn't have any effect. As shown in Figure 28, different concentrations of RHAMM sequence ~~(423-432-AA)~~(aa. 423-432) progressively inhibited migration of human fibroblasts up to 40%.

Please replace the paragraph beginning at page 94, line19, with the following amended paragraph:

Both treatments were successful in inhibition of cell migration *in vitro*. These important data suggests potential implementation of the both P-peptide and RHAMM sequence ~~423-432 AA peptide~~aa. 423-432 peptide in prevention of tissue contraction and fibrosis and ultimately prevention of abnormal tissue remodeling and scaring.

Please replace the paragraph beginning at page 96, line 6, with the following amended paragraph:

Briefly, mouse normal and RHAMM knockout fibroblasts are plated in DMEM medium and starved overnight. Medium was changed and two different concentrations of PDGF added. After 10 min cells were lysed in RIPA (RIPA comprises 150mMNacl, 1.0% IgepalCA-630, 0.5% sodium deoxycholate, 0.1% SDS, 50mMTris, pH 8.0) buffer. Western blot analysis was done and proteins separated by SDS-PAGE. Bands were visualized by phospho-specific erk antibody. Subsequently, blot was stripped and reprobed with erk antibody.

Please replace the paragraph beginning at page 100, line 4, with the following amended paragraph:

This experiment determines which cell type from synovial fluids of ~~RA~~ rheumatoid arthritis (RA) patients express RHAMM isoforms.

Please replace the paragraph beginning at page 100, line 6, with the following amended paragraph:

Briefly, samples of synovial fluids from different RA patients were centrifuged at 1600 rpm's for 10 min and pellets resuspended in 2-5 ml of Blocking buffer (BB, 1% human serum albumin in ~~HBSS~~ Hank's buffered salt solution (HBSS). After counting, 10^6 to $2.5x10^6$ cells per ml, were taken into each tube. Cells were washed once with 1ml of BB and the pellets resuspended in 100 µl of BB. First antibody was added (dil. 1:100) and samples incubated for 30 min on ice. Along with the first antibody 20 µl of specific markers for certain cell type present in the synovial fluid were added, as well. Rabbit IgG was used as a control. Samples were

washed twice with 1 ml of BB. After washing, secondary antibody was added (~~FITC~~ fluorescein isothiocyanate (FITC), dil. 5:100) and cells kept 30 min on ice. Again, samples were washed twice, each time with 1 ml of BB and fixed with 0.3 ml of 0.5% paraformaldehyde. Immunofluorescence was determined by flowcytometre.

Please replace the paragraph beginning at page 101, line 9, with the following amended paragraph:

In order to investigate if there is any RHAMM expressed in the synovium tissue of RA patients, immunohistochemistry was done. Briefly, pannus formed from synovium tissue was isolated and embedded in wax. Three microns tissue sections were obtained and slides were heated on 58°C for 30 min. To deparafinized slides the following procedure was done: tissue sections were washed in xylene three times each four minutes. After washing in hylene, slides were washed in 100% ethanol two times each three minutes. Additionally sections were washed in 96% ethanol the same amount of time. Slides were then incubated in dH_2O two times each three minutes and once in PBS. Tissue on the slides was then marked with barrier-pen. The activity of endogenous peroxidase was blocked with 0.3% of hydrogen peroxide for 10 min. Slides were washed with dH20 two times each 3 minutes and with PBS two times each 5 minutes. Unspecific binding was blocked with 1% bovine serum albumin (BSA) in PBS at 37°C for 30 minutes. Different dilutions of RHAMMv4 and RHAMM R3.8 antibodies were made: 1:100, 1:50, 1:25) in 1% BSA-PBS and incubated with tissue samples overnight at +4°C. Two tissue sections served as controls and they were incubated with either rabbit IgG (at the same dilution as the antibodies) or with vehicle which was 1%BSA PBS, without primary antibody. After incubation with primary antibodies, slides were washed with PBS three times, 10 minutes each. Consequently, biotinylated antirabbit IgG was added and slides kept at room temperature for 1 hour (dil.1:200 in BSA-PBS). Slides were again washed with PBS three times each 10 minutes. Additionally, Avidin-biotin ~~ABC~~ avidin peroxidase conjugate (ABC) reagent was premixed and incubated with slides at room temperature for one hour. Slides were washed with PBS three times each 5 minutes. After washing, ~~DAB~~ diaminobenzidine (DAB) solution

was premixed and incubated with slides for 5 minutes at room temperature. Samples were washed with dH_2O three times each time 5 minutes and counterstained with hematoxylene for 1-2 minutes. Samples were washed with regular water and dehydrated. For dehydration similar procedure was done as for deparafinization only this time steps were done backwards. Slides were mounted and left to dry overnight.

Please replace the paragraph beginning at page 105, line 12, with the following amended paragraph:

C. ~~RT-PCR~~ Reverse Transcriptase Polymerase Chain Reactor Analysis (RT-PCR)

Frozen wound samples (50-100 mg tissue) were homogenized in 1 ml of Trizol reagent and RNA was isolated according to standard Trizol Reagent Protocol. For the synthesis of oligo-dT-primed cDNA, 2μg of total RNA, 1 μg of oligo(dT) primers and Moloney Murine Leukemia Virus Reverse Transcriptase (Gibco Brl # 28025-013) were used. Following 1 h incubation at 37°C, the reaction was stopped by heating samples at 95°C for 5 min and 2 μl of RT reaction mixture was used for PCR. PCR amplification was performed with platinum Taq DNA polymerase (Gibco BRL #10966-018) and specific primers for collagen I and III were used: 5' CGA TGT CGC TAT CCA GCT GA (SEQ ID NO:52) for collagent I and the following primer 5' ATC AGT CAG CCA TCT ACC ACC (SEQ ID NO:53) was used for collagen type III. Thermal cycles for collagen type I and III were as follows: denaturation at 94°C, annealing at 60°C and polymerization at 72°C for 20 cycles. In addition, a set of primers of a common housekeeping gene B-actin, were run in parallel on 1.5% agarose gel as a loading standard.

Please replace the paragraph beginning at page 107, line 17, with the following amended paragraph:

C. RT-PCR Analysis

Frozen wound samples (50-100 mg tissue) were homogenized in 1 ml of Trizol reagent and RNA was isolated. For the synthesis of oligo-dT-primed cDNA, 2 μg of total RNA, 1 μg of oligo(dT) primers and Moloney Murine Leukemia Virus Reverse Transcriptase (Gibco Brl

#28025-013) were used. Following 1 h incubation at 37°C, the reaction was stopped by heating samples at 95°C for 5 min and 2 µl of ~~RT~~ reverse transcriptase (RT) reaction mixture was used for PCR. PCR amplification was performed with platinum Taq DNA polymerase (Gibco BRL #10966-018) and specific primers that used for ED-1 is: for ED-1 –5' CGA TGG CAG GAC AGT AGT CGC (SEQ ID NO:54) and/or 5' AAG GCT GCT GTT GAA AGG ACG (SEQ ID NO:55).

Please replace the paragraph beginning at page 109, line 3, with the following amended paragraph:

This experiment investigates whether functional expression of the HA receptor RHAMM is required for enhancement of ~~CaP~~ prostate cancer cells (CaP) cell motility and invasion *in vitro*.

Please replace the paragraph beginning at page 109, line 5, with the following amended paragraph:

Briefly, Dunning CaP cell lines (AT-1, MatLyLu) were grown in ~~DMEM~~ Delbeco's modified Eagle's medium (DMEM) medium supplemented with 10% FBS at 37°C in a humidified atmosphere containing 5% CO_2~~containing 5% CO2~~. All cell lines were passaged every 3-4 days upon reaching confluency.

Please replace the paragraph beginning at page 109, line 15, with the following amended paragraph:

B. Western blotting.

Cells were also grown to 50-60% confluency were lysed using RIPA buffer. Equal amounts of total cell protein were loaded onto a 10% SDS-PAGE gel. RHAMM was probed using a polyclonal antibody to the C-terminus (Zram, 1:1000) and ~~HRP~~ horseradish peroxidase (HRP)-conjugated goat anti-rabbit antibody (1:5000). RHAMM was visualized by chemiluminescence.

Please replace the paragraph beginning at page 110, line 7, with the following amended paragraph:

E. ~~MMP~~ Matrix Metaloproteases (MMP) activity.

Cells were grown to confluency in growth media, detached and equal number of cells were seeded in 6-well plates uncoated or coated with 50% Matrigel in media. Cells were allowed to adhere for 1h to the substrate, and then treated with the peptide mimicking the HA-binding domain of RHAMM (100 μg/ml) for 24 h in serum-free media. The activity of MMP secreted into the media was determined by zymography using 8% SDS-PAGE.

Please replace the paragraph beginning at page 117, line 5, with the following amended paragraph:

In addition to specific peptides such as those described in ~~SEQ. ID NOS: 1-10~~SEQ ID NOs: 1-10 that represent hyaladherins which bind to hyalauronic acid, a variant of additional polypeptides may be identified, generated and tested for use within the methods described herein. All such binding motifs are characterized by the presence of general amino acid motifs including staggered basic residues. These motifs can be more generally described as BX7B (SEQ ID NO:28) where B is any basic amino acid and X7 is any amino acid sequence of about seven residues but usually including at least one hydrophobic amino acids or an additional basic amino acid. Most importantly however, none of the intervening X amino acids should be acidic, as acidic amino acids appear to interfere with binding to hyalauronan, a negatively charged polymer. Peptides which are specifically excluded from this motif include: BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK ~~(SEQ ID Nos. 29-44 respectively)~~(SEQ ID NOs: 29-44 respectively). These excluded peptides do not bind HA with the same high affinity as peptides of the present invention which require are peptides that form an alpha helix. All motifs that bind to hyalauronan also preferably form strong alpha helices as predicted in secondary structure protein analysis programs which further

show that hyalauronan binding motifs contain at least two basic amino acids aggregating along one plane of the helix.

Please replace the paragraph beginning at page 123, line 26, with the following amended paragraph:

Briefly, Dunning CaP cell lines (AT-1, MatLyLu) were grown in DMEM medium supplemented with 10% FBS at 37°C in a humidified atmosphere containing ~~5% CO2~~5% CO_2. All cell lines were passaged every 3-4 days upon reaching confluency.

Please replace the paragraph beginning at page 126, line 28, with the following amended paragraph:

These results indicate that RHAMM and its major ligand HA associate functionally with autoimmune insulitis leading to ~~IDDM~~ insulin dependent diabetes mellitus (IDDM), and that by using specific RHAMM peptides they can serve as potential therapeutic targets.